- The claimed nucleic acids are not supported by a specific asserted utility because the disclosed nucleic acids are not linked to the diseases discussed within the specification on pages 17 and 18.

Applicants respectfully submit that the asserted utility is the use of the composition in the "diagnosis of conditions, disorders, and diseases associated with the immune system and immune response" as stated on page 1, lines 6 and 7. The claimed composition comprises a plurality of polynucleotides which represent cDNAs on microarrays that were at least two-fold differentially expressed in response to cytokine treatment of PBMCs in experiments carried out prior to the filing of the application.

The role of cytokines in immune disease and immune response is well known in the literature (textbooks cited on page 1, lines 10-13 and 24-25, and articles that were provided to the Examiner with the 1449), and several disorders were specifically discussed in the background of the invention. The disorders specifically associated with pro-inflammatory cytokine treatment are set forth on page 4, lines 5-7 and in claim 19. They are viral infections, rheumatoid arthritis, Crohn's disease insulin-dependent diabetes mellitus, encephalomyelitis, inflammatory bowel disease, multiple sclerosis, pemphigus vulgaris, and psoriasis. Similarly the disorders associated with anti-inflammatory cytokine treatment were set forth on page 4, lines 7-9 and in claim 20. They are allergies and atopic disorders, bacterial and parasitic infections, chronic graft versus host disease, scleroderma, and systemic lupus erythematosus.

Applicants have amended claim 1 to recite, "A composition comprising a plurality of polynucleotides whose expression is modulated by cytokines, wherein the polynucleotides are SEQ ID NOs:1-516 or a complete complement of SEQ ID NOs:1-516".

- The claimed nucleic acids are not supported by a substantial utility because no substantial utility has been established for the claimed subject matter...a starting material that can only be used to produce a final product does not have a substantial utility...a "real world" context or use.

Applicants submit that the claimed invention is a composition comprising a plurality of polynucleotides which represent cDNAs which were more than 2-fold differentially expressed in response to pro- or anti-inflammatory cytokine treatment of PBMCs. The polynucleotides of the claimed combination were laboriously selected from the analysis of expression profiles. An expression profile is produced by comparison of data from the hybridization of microarrays, each containing about ten thousand cDNAs, with treated and untreated samples. The expression profiles and their uses were described in the specification beginning on page 18, line 30 and ending on page 19, line 18.

The expression profiles that resulted from the treatment of PBMCs with pro- and anti-inflammatory cytokines allowed identification of differentially expressed novel and known polynucleotides. In fact, the inventors were able to assign new roles (and their pro- or anti-inflammatory disease associations) to some well known genes. In EXAMPLE VIII, on page 30, lines 22-24, the specification

recites, "Other genes identified in table 4, such as thrombomodulin, the mucin-like hormone receptor EMR1, and the LIM protein ESP1/CRP2, were not previously known to be modulated by cytokines."

Applicants respectfully submit that the use of the composition, comprising a plurality of polynucleotides selected from expression profiles from microarray experiments, to diagnose immune diseases or to monitor immune response has an immediate and beneficial "real world" use.

In further support of the utility of the composition, the expression pattern of individual polynucleotides can be associated with pro- or anti- inflammatory diseases, Applicants have provided the DECLARATION UNDER 37 CFR 1.132 OF SUSAN G. STUART. Dr. Stuart uses transcript images, a second and independent method that also produces an expression profile and was mentioned on page 22, line 14 of the specification, to support the disease associations for SEQ ID NO:173 (first line of Table 2, anti-inflammatory cytokines) and reluctantly elected novel sequence, SEQ ID NO:219 (first line of Table 3, pro-inflammatory cytokines). These polynucleotides were chosen because of their demonstrated 3.56 vs 0.14 and 3.94 vs 0.49 differential expression after anti-inflammatory and pro-inflammatory cytokine treatments, respectively. Dr. Stuart has shown that the expression of SEQ ID NO:173, which was induced by pro-inflammatory cytokines as defined on page 5, lines 27 and 28 of the specification, is clearly associated with rheumatoid arthritis, a pro-inflammatory disorder as listed on page 4, lines 5-7 of the specification. Similarly, Dr Stuart has shown that the expression of SEQ ID NO:219, which was induced by anti-inflammatory cytokines, is clearly associated with metastatic colon cancer. When used in a tissue specific and clinically relevant manner with biopsied samples, SEQ ID NO:219 is clearly diagnostic of a metastatic colon cancer, an invasive, and therefore, anti-inflammatory disorder.

- Neither the specification as filed nor any art of record discloses or suggests any property or activity for the nucleic acid and/or protein

Applicants submit that it is not necessary to know any property of the nucleic acids or even whether they encode proteins to use them in the claimed composition. The specification clearly stated in THE INVENTION section and again beginning on page 29, line 32, and ending on page 30, line 2, "Since the polynucleotides were identified solely based on differential expression in cytokine-treated versus untreated tissue, it is not essential to know a priori the name, structure, or function of a particular gene or protein". Each polynucleotide has one known activity, differential expression under cytokine stimulation, and that activity is the basis for its utility as a diagnostic of an immune disorder or response.

With the clarification of claimed invention and its asserted utility, the DECLARATION UNDER 37 CFR 1.132 OF SUSAN G. STUART, and the amendment of claim 1, Applicants respectfully request that the rejection of claims 1, 6-7, and 18-20 under 35 USC § 101 be withdrawn.

CLAIM REJECTIONS - 35 USC § 112

The Examiner has rejected claims 1, 6-7, and 18-20 under 35 USC § 112, first paragraph, since the claimed invention is not supported by either a specific, substantial and credible utility or alternatively, a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention. The Examiner states:

- "that SEQ ID NO:219 corresponds in some undefined way to a cDNA/genomic cDNA encoding human species of protein/nucleic acid"
- that the polynucleotides of the composition comprise gene sequences and fragments sequences of SEQ ID NO:219 and complements thereof
- the claimed composition includes possible flanking sequences

Applicants submit that SEQ ID NO:219 is a highly differentially expressed and novel polynucleotide which is one element of the claimed composition. It is a human cDNA which was cloned from an expressed mRNA as described in the EXAMPLES of the specification. By definition, it has no introns, no promoter, and no flanking genomic sequence. Applicants further submit that it is a useful element of the composition, and no encoded peptide was described in the specification or sequence listing nor claimed.

Applicants have amended claim 1 as shown above so that the composition does not claim gene sequences or fragments sequences of SEQ ID NO:219.

With the withdrawal of the 35 USC § 101 rejection and the arguments above, Applicants respectfully request that the rejection of claims 1, 6-7, and 18-20 under 35 USC § 112, first paragraph, be withdrawn.

The Examiner has rejected claims 1, 6-7, and 18-20 under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner states that the claims are indefinite by the limitation "a complement".

Applicants have amended claim 1 as shown above to clarify the invention. With this amendment, Applicants respectfully request that the rejection of claims 1, 6-7, and 18-20 under 35 USC § 112, second paragraph, be withdrawn.

CLAIM REJECTIONS - 35 USC § 102

The Examiner has rejected claim 1 under 35 USC § 102 (b) as being anticipated by products O 6003 and O3753 of the 1990 Sigma Chemical Catalog in view of the 35 USC § 112, second paragraph, rejection concerning the metes and bounds of "a complement". The Examiner states that these products are poly d (T) oligomers with 88%-93% identity to SEQ ID NO:219 or its complement.

Applicants have amended claim 1 as shown above to clarify the invention.

With the amendment of claim 1, Applicants respectfully request that the rejection of claim 1 under 35 USC § 102(b) be withdrawn.

DECLARATION OBJECTION

The Examiner has stated that the oath/declaration was not signed and dated by the named inventors.

Applicants will provide a signed declaration under separate cover as soon as possible. One of the inventors will not return from Australia until mid-February.

CONCLUSION

Applicants submit that the present application is now in condition for allowance. If a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent directly at (650) 845-4159. Applicants believe the no further fee is due; however, if the Commissioner determines that any fees are required, the Commissioner is hereby authorized to charge, or credit any overpayment, to Incyte Genomics, Inc. Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE GENOMICS, INC.

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Please amend claims 1, 7, 8, 18, and 20 as shown below.

For the Examiner's convenience, all pending claims are shown below.

1. (Once Amended) A composition comprising a plurality of polynucleotides whose expression is modulated by cytokines, wherein the polynucleotides are [comprise] SEQ ID NOs:1-516 or a complete complement of SEQ ID NOs:1-516 [thereof].

6. The composition of claim 1, wherein the polynucleotides are immobilized on a substrate.

7. (Once Amended) A [high throughput] method for detecting a polynucleotide in a sample, the method comprising:

a) hybridizing the composition of claim 1 with the sample, thereby forming at least one hybridization complex; and

b) detecting the hybridization complex, wherein the presence of the hybridization complex indicates the presence of the polynucleotide in the sample.

8. (Once Amended) A [high throughput] method of screening a library of molecules or compounds to identify a ligand, the method comprising:

a) combining the composition of claim 1 with a library of molecules or compounds under conditions to allow specific binding; and

b) detecting specific binding, thereby identifying a ligand.

9. The method of claim 8 wherein the library is selected from DNA molecules, RNA molecules, peptide nucleic acids, mimetics, peptides, and proteins.

18. (Once Amended) A method of screening a sample from a patient for an immune response, disorder, condition, or disease, the method comprising:

a) contacting the sample with the composition of claim 1 immobilized on a substrate under conditions to allow formation of a hybridization complex;

b) [detecting and] quantifying complex formation; and

c) comparing complex formation with a standard, wherein a change in the amount of complex formation indicates the presence of the immune disorder, condition, or disease.

19. The method of claim 18, wherein the immune disorder, condition, or disease is a pro-inflammatory disorder selected from viral infections, rheumatoid arthritis, insulin-dependent diabetes mellitus, multiple sclerosis, encephalomyelitis, inflammatory bowel disease, psoriasis, and pemphigus vulgaris.

20. (Once Amended) The method of claim 18, wherein the immune [system] disorder, condition, or disease is an anti-inflammatory disorder selected from bacterial and parasitic infections, allergies and other atopic disorders, chronic graft versus host disease, scleroderma, and systemic lupus erythematosus.